

**Implementation of new echocardiographic modalities in routine
practice in a general hospital – Pocket-size cardiac ultrasound and
3 dimensional echocardiography.**

Studies on feasibility and diagnostic accuracy

Vidar de Bourg Ruddox

Thesis for the degree of Philosophiae Doctor

Department of Cardiology, Vestfold Hospital Trust

&

University of Oslo, Faculty of Medicine

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Vidar de Bourg Ruddox, January 2015

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1 Synopsis

This thesis is based upon the implementation of pocket-size cardiac ultrasound (PCU) among medical students and residents in internal medicine and 3 dimensional echocardiography (3DE) in routine care at a general hospital.

The introduction of widely available and handy ultrasound devices has represented a challenge to the medical community as implementation in clinical practice can be made by non-specialists. In view of favorable results from the non-expert use of the larger laptop-sized devices, the thesis at hand aimed at evaluating the feasibility and diagnostic accuracy of PCU. Twenty one medical students and 26 internal medicine residents performed PCU at Oslo University Hospital, Rikshospitalet and Vestfold Hospital Trust respectively. After a brief 4 hour training with a Vscan device the medical students could detect mitral regurgitation significantly better than with a physical examination alone. Left ventricular (LV) dysfunction was detected with high sensitivity, whereas detection of aortic regurgitation and aortic stenosis did not improve. PCU was used infrequently by the 26 medical residents after only 2 hours of training, and with an overall low sensitivity to detect disease. In view of a high specificity and negative predictive value, the PCU method, however, could provide a suitable means of ruling out significant disease.

3DE, the more advanced contemporary echocardiographic technique available, is at present more relevant than before due to faster acquisition and imaging. Thus, it has the potential to replace traditional 2 dimensional echocardiography (2DE) in cardiology care. To explore this, we performed a systematic literature search of studies comparing transthoracic 3DE with a standard 2DE in the evaluation of valvular heart disease and LV function. We found that 3DE was to be recommended rather than 2DE in usual patient care in order to evaluate cardiac LV

volumes and ejection fraction (EF). These two parameters are considered to be essential in the therapeutic and prognostic assessment of several cardiac disorders.

3DE does, however, require better image quality and regular heart rhythm in the assessment of cardiac disease, and the search we performed did not adequately answer how many could not be examined with the 3DE technique.

To that end, we designed a study of consecutive patients who had been through successful LV assessment by PCU, 2DE and 3DE. Of 273 patients successfully examined with PCU and 2DE, only 202 (74%) had satisfactory 3DE images. Contrary to many other studies in this field, a significant overestimation of LV volumes was observed in 2DE compared to 3DE, whereas no such difference was found for LV EF. We conclude that 2DE is still an important tool for LV studies and that it is essential to introduce concise recommendations for endocardial tracing of the LV cavity for both 2DE and 3DE echocardiography.

2 Scientific environment

The Department of Cardiology at Vestfold Hospital Trust has been involved in several studies of 2DE. The DEFIANT II Study of LV remodeling in post-myocardial infarction [1] and the Left ventricular remodeling study (LEVEREM) [2] of follow up of 834 post-infarction patients are two such renowned studies. The department has conducted a study of accuracy and reproducibility of 2DE LV volume and EF measurements [3], and in the years 2006 – 2008 normal reference studies of 3DE measurements of all 4 heart chambers [4-6] were performed.

Department of Cardiology at Oslo University Hospital, Rikshospitalet has a comprehensive research record within the field of cardiovascular imaging. Professor Thor Edvardsen is the Head of this department, and also Head of the Center for Cardiological Innovation. This center has the objective of developing the next generation of ultrasound systems for cardiology and to that end has been awarded a grant as a Centre for Research-based Innovation by the Research Council of Norway. At present, Professor Edvardsen also chairs the European Association of Cardiovascular Imaging's (EACVI) Scientific Documents Committee.

3 List of Papers

Paper I

Stokke TM, Ruddox V, Sarvari SI, Otterstad JE, Aune E, Edvardsen T. Brief Group Training of Medical Students in Focused Cardiac Ultrasound May Improve Diagnostic Accuracy of Physical Examination. *J Am Soc Echocardiogr* 2014;27:1238-46

Paper II

Ruddox V, Stokke TM, Edvardsen T, Hjelmæsæth J, Aune E, Bækkevar M, Norum IB, Otterstad JE. The diagnostic accuracy of pocket-size cardiac ultrasound performed by unselected residents with minimal training. *Int J Cardiovasc Imaging* 2013;29: 1749-1757

Paper III

Ruddox V, Mathisen M, Bækkevar M, Aune E, Edvardsen T, Otterstad JE. Is 3D echocardiography superior to 2D echocardiography in general practice?

A systematic review of studies published between 2007 and 2012. *International Journal of Cardiology* 2013;168: 1306–1315

Paper IV

Ruddox V, Edvardsen T, Bækkevar M, Otterstad JE. Measurements of left ventricular volumes and ejection fraction with three-dimensional echocardiography; feasibility and agreement compared to two-dimensional echocardiography. *Int J Cardiovasc Imaging* 2014;30: 1325-30

4 Abbreviations and Acronyms

PCU	Pocket-size cardiac ultrasound
3DE	Three dimensional echocardiography
LV	Left ventricle/left ventricular
2DE	Two dimensional echocardiography
EF	Ejection fraction
LEVEREM	Left ventricular remodeling study
EACVI	European Association of Cardiovascular Imaging
HCU	Hand-carried ultrasound
FCU	Focused cardiac ultrasound
ASE	American Society of Echocardiography
FoCUS	Focus cardiac ultrasound
SE	Standard echocardiography
EAE	European Association of Echocardiography
FEEL	Focused echo evaluation in life support
FATE	Focussed assessed transthoracic echocardiography
CMR	Cardiac magnetic resonance
PRISMA	Preferred reporting items for systematic reviews and meta-analyses
PE	Physical examination
PPV	Positive predictive value
NPV	Negative predictive value
EDV	End diastolic volume
ESV	end systolic volume

We have identified more than 20 abbreviations and acronyms for the ultrasound devices enabling hand-held operation. These abbreviations and acronyms sometimes describe the actual device, sometimes its operation or operator/device interaction or both. Throughout this thesis we have chosen the term pocket-size cardiac ultrasound, PCU, reflecting both the device and its use. However, when discriminating between the contemporary pocket-size devices and the laptop-size devices, we use PCU for the former and hand-carried ultrasound (HCU) for the latter. In paper I the term focused cardiac ultrasound (FCU) was used as requested by the respective editorial office. At present, FCU is used by the American Society of Echocardiography (ASE). However, PCU is used consistently when paper I is referred to throughout this thesis. After all the studies which make up this thesis were completed, the EACVI introduced the term Focus cardiac ultrasound (FoCUS), which focuses upon the operation but not the device itself.

5 Introduction

5.1 Background and motivation

In recent years imaging modalities previously seen as rarities have become more commonly available for general cardiology practice; PCU and real-time 3DE. The purpose of the present thesis, which was designed in 2010-2011, was to evaluate the clinical utility of PCU when used by non-cardiologists with limited training and to assess the potential of introducing transthoracic 3DE in routine care in a general hospital as compared with the present standard, the 2DE.

5.1.1 Pocket-size cardiac ultrasound

In the previous 10-year period hand-held devices with the size of laptop computers have been available for quick look bedside cardiac imaging. Thus expanding the use of echocardiography, as the full size echocardiographic equipment has practical limitations for use outside the echo laboratory. These laptop computers often referred to as HCU are still rather large and have to be transported on wheels. They should therefore be distinguished from the more recently developed and smaller pocket-size devices.

Ultrasonic real time imaging with a hand-held scanner was introduced by Ligtoet et al. in 1978 [7], with the first clinical experiences described by Roelandts et al. [8]. The quality of images was comparable to conventional linear array scanners of that time. Later studies have reported upon the development of laptop-sized scanners including color Doppler [9-12]. Bedside examinations by various categories of operators, including internal medicine residents and cardiologists, have given considerable additional information to physical examination in elective [13-17] and emergency [18] care, even with limited training and sparse echocardiographic experience.

The smallest cardiac ultrasound machines today, the pocket-size imaging devices, have been available since 2009. The term refers to the ability of the apparatus to fit in a pocket and its limited functions, and serves to distinguish them from the larger and more complex portable, mobile and stationary devices [19].

When the studies in this thesis were designed very little data were available on the use of PCU by non-cardiologists with limited training, such as residents on call in internal medical departments of general hospitals, or by medical students in University teaching hospitals. Unresolved issues were the level of training required for non-echocardiographers to use these machines in patient management, if such an introduction could and should take place at medical school or during clinical work, and to what extent such a practice would represent a benefit versus a potential danger to the patient.

This thesis investigates the implementation of PCU by applying minimal training for medical students and residents in internal medicine.

5.1.2 Three dimensional echocardiography

The 3DE, once reserved for research purposes, has evolved towards smaller size, faster imaging processing and better utility. The introduction of real time 3DE has thus represented the potential for this technique to be used in outpatient clinics and regular patient management outside the research lab and invasive centers, devoid of the limitations 2DE display. In particular, transoesophageal 3DE has proven its value with excellent visualization of mitral valve morphology for optimal reconstruction of regurgitant lesions, guidance during surgery and catheter-based procedures and such. With the transthoracic approach, however, the situation was different, and a long-standing debate on possible advantages over 2DE in common practice still existed when our studies were designed.

Even though our department has made use of 3DE for research purposes for years [4-6], the modality has so far not gained use in our routine practice. The reasons put forward by our cardiologists are the steep learning curve and the challenge to obtain good images in certain categories of patients.

Since there was diverging views on the clinical benefit of transthoracic 3DE versus 2DE in general hospital practice, this thesis aimed at comparing in the same patients the techniques being applied. First, we planned to undertake a systematic literature search of such comparisons, where a *gold standard* had been used for reference. Second, we designed a prospective study of consecutive patients admitted to our department, and who had their LV systolic function measured by 2DE followed by a subsequent 3DE.

5.2 Review of research

5.2.1 Pocket-size cardiac ultrasound

As early as 2002 the ASE published recommendations for hand-carried ultrasound [20], although limited data was available at the time. These HCU devices had full size or near full size echocardiographic capabilities, as opposed to the smaller PCU devices. According to Lucas et al. [21] the ASE replicated the contemporary training recommendations for standard echocardiography (SE), such that all HCU trainees were expected to perform 75 echocardiographic examinations and 150 interpretations. In the years following, however, excellent HCU performance (as evaluated by subsequent SE) was reported by examiners with less training [13, 21, 22].

In 2011 the European Association of Echocardiography (EAE) produced a position paper providing recommendations on the definition of PCU and its usage in the clinical arena [19]. Key points in this statement were that PCU does not provide a complete echocardiographic examination and that the imaging assessment should be reported as part of the physical

examination. With the exception of fully trained cardiologists, specific training and certification was recommended for all users. In this context specific training and revision of basic cardiac physiology and pathology knowledge should be mandatory. No further details were presented, and the training level selected for participants in the present studies was therefore highly arbitrary.

Within the studies precipitating this thesis there was widespread support for the expert usage of PCU [23-26]. There were concerns, however, about the utility of PCU when undertaken by non-cardiologists with limited training [27]. Possible misdiagnoses of cardiac disorders could result in serious consequences for patients.

The aim was to find a level of training for a large group of medical students or junior doctors which was both economically feasible and safe in terms of patient management. Two frameworks for the use of echocardiography in critically ill patients have been designed and validated; the FEEL (focused echo evaluation in life support) protocol [28] and the FATE (focussed assessed transthoracic echocardiography) protocol [29], but not for the training of residents in internal medicine and medical students.

When the studies on PCU were designed at the end of 2010, a search of the literature only detected two studies reporting an evaluation of the use of PCU by non-cardiologists with limited training, one performed by residents in internal medicine [30] and one by a single cardiology fellow [31]. These studies, although heterogeneous in design, were principally based upon selected PCU operators. They unmasked a need for more studies; no cut-off point for the education level of trainees could be identified and no outcome data were available.

We explored the training levels applied in these two PCU studies. The training program in the study of Galderisi et al. [30] included 15 hours of instruction on the basic principles of cardiac ultrasound and 3 months (3 times per week, 12 examinations per day, totalling 145-150

examinations) of handling and visual interpretation of PCU examinations with exclusively visual judgements of limited parameters. In the study of Culp et al. [31] the selected cardiology fellow had completed 2 months of dedicated echocardiography training including approximately 120 formal TTE acquisitions. Additionally, the fellow was acquainted with the operation of the PCU device used and had more than 30 acquisitions with this device.

Studies wherein medical students used PCU were not detected, and we thus had to look back to the older HCU literature. Wittich and coworkers introduced an echocardiography training program to 42 medical students in 2001 [32]. Training consisted of 90 minutes of introduction, 60 minutes of small-group training and a mean 14 minutes of independent practice and feedback. Students were asked to identify cardiac structures in a parasternal long axis view before and after training, resulting in an increase in correct labelling from 3.7% to 91.0% as well as an increased image quality. The authors concluded that availability of handheld ultrasound devices during clinical clerkship would provide students with a technology that could one day be an extension of the physical examination. Four years later, DeCara et al [33] reported that a limited training protocol improved the ability of 10 fourth-year medical students to perform correct bedside diagnosis as compared to the physical examination alone.

The training levels in these studies mentioned above [13, 15, 21, 22, 30-34] ranged from two and three to several hours, all with acceptable results. We had these studies in mind when deciding training protocols for PCU operators.

5.2.2 Three dimensional echocardiography

A prerequisite in many of the studies preceding this thesis was that patients had a regular heart rhythm. Due to technical limitations of the 3DE technique, it is not possible to obtain one-beat full volume acquisitions in the same way as for 2DE and still maintain the frame rate

(frames per second) needed for high resolution imaging. As a workaround, the 3DE technique uses multiple beat acquisitions from consecutive heart cycles to stitch together a full three dimensional volume from several smaller volumes, typically 4 to 6 heart cycles. The technique therefore calls for steady imaging without irregularities neither temporally or spatially, hence the need for patients with regular heart rhythm who are able to hold their breath for some time such that 3DE is feasible.

In a 2007 feasibility study of 3DE in routine practice [35], 3DE was technically feasible in 83% of 168 unselected patients. In this context, feasibility was defined as the ability for 3DE to measure LV parameters and reasons for exclusion were poor image quality (n=24/168), failure of ECG-triggering (n=3/168) and unknown in one patient. If the image quality was poor due to irregular heart rhythm, failure to hold breath, poor acoustic window/*echogeniety* or some other reason was not reported.

During the period when real time 3DE became available to clinicians, Mark J. Monaghan described a set of key points for 3DE evaluation of the left ventricle [36]. He pointed out that both M-mode and 2DE make important assumptions about the LV which lead to inaccuracies in measurements. A poor inter- and intra-observer variability limits the use of the 2DE technique in scientific studies and in follow-up of patients. Further, the combination of new instrumentation and software programs to analyze 3D datasets of the LV had been shown to provide highly accurate analysis of its morphology and function (compared to cardiac magnetic resonance [CMR]). He therefore advocated 3DE as the first choice technique for noninvasive evaluation of the LV.

In our own experience the reproducibility of LV volumes and EF was better with 3DE than 2DE in normal individuals with sinus rhythm [6]. This was supported in two studies by Jenkins et al. [37, 38].

At the time this thesis was planned there were no guidelines for the preferred use of transthoracic 3DE versus 2 DE in various cardiac disorders. Existing 2006 EAE recommendations for chamber quantification recommended the 2DE biplane method of discs (modified Simpsons rule) to assess LV volume and EF [39].

5.3 How can our studies contribute to new knowledge about the implementation of these modalities in common practice?

5.3.1 PCU – 2 studies

An interesting challenge following the introduction of pocket-sized devices was to incorporate their use in the education of medical students doing their term in cardiology. The low costs and simplified operation have opened for the potential use of these devices by nontraditional cardiac ultrasound users. Since few studies had evaluated PCU performed by a large group of medical students we wanted to investigate whether a brief, group based PCU training course would allow them to improve their ability to detect clinically relevant cardiac lesions at the bedside, using a subsequent SE performed by an experienced echocardiographer as reference. Such knowledge would be of importance in the decision to include PCU as part of the cardiological education of medical students.

Although the EAE has stated that PCU does not represent a complete echocardiographic examination, the new devices may represent a tool for rapid point-of-care decision making [19]. In many Norwegian hospitals, 24/7 cardiology service with immediate SE is not established, and many patients admitted outside of working hours will not undergo SE until either the next day or the following Monday when hospitalized at week-end. In the second study the purpose was to assess the performance of PCU when used by unselected residents working on-call in a medical department after a short period of training. As a reference standard, a subsequent blinded SE conducted by an experienced echocardiographer was used.

Knowledge of the performance of PCU could be of importance in deciding whether or not to implement a routine where all residents on call have sufficient training to obtain valuable information from PCU in an emergency setting.

5.3.2 3DE – 2 studies

As no guidelines for the preferred use of transthoracic 3DE versus 2 DE in various cardiac disorders had been produced, we decided to perform a systematic search of studies comparing the two methods to explore whether 3DE systems perform better than 2DE in the transthoracic assessment of LV volumes and valvular disease, the two most common indications for doing echocardiography in a general hospital. A prerequisite for including studies was that the two methods had been matched against a reference method. We suspected that 3DE would perform better than 2DE in these assessments, but that the comparisons had only been undertaken in selected patients with regular heart rhythm and with good quality 3DE images.

Additionally we designed a prospective study comparing these two techniques. Since this thesis aims to reflect everyday practice in a general hospital, we decided to include the consecutive patients who had undergone a PCU on admission, and then have them undergo a subsequent 2DE with measurement of LV volumes and EF with the biplane Simpson's method. They were then to be examined with 3DE assessment of the same variables. As the review described above did not provide clear evidence supporting the use of 3DE for valve disorders, the study did not include any such comparison. With the 3DE problems already mentioned we wanted to establish the percentage of patients eligible for a successful LV study by 3DE and explore the main reasons for the failure to acquire these measurements. In addition, we also wanted to explore possible differences in LV volumes and EF obtained with the two methods.

The information sought might be of importance in future patient management and in an eventual decision to abandon 2DE and implement 3DE as the main echocardiographic tool in common practice, and if the same reference and cut-off values can be applied to both methods.

5.4 Summary of introduction

The present thesis incorporates a critical evaluation of the implementation of two ultrasound modalities; PCU performed by medical students and residents on call in a general hospital, and transthoracic real time 3DE LV volume measurements compared with 2DE performed by experienced echocardiographers. The results may be helpful in the decision making as to whether to introduce PCU on a broad scale among non-cardiologists with minimal training, and eventually give support for a more general use of transthoracic 3DE at the cost of 2DE.

6 Aims of the thesis

1. To investigate whether a brief, group-based PCU training course would allow medical students to improve their ability to detect clinically relevant cardiac lesions bedside.
2. To assess the diagnostic accuracy of PCU, expressed in terms of sensitivity, specificity, predictive values and agreement, when used by unselected residents working on-call in a medical department.
3. Perform a systematic literature search to explore whether 3DE systems perform better than 2DE in the transthoracic assessment of LV volumes and valvular disease.
4. To determine the feasibility of 3DE for LV studies already completed by 2DE in patients at a general hospital and to explore the correlation between the two methods.

7 Materials and methods

7.1 Study populations and methods

The studies of PCU in papers I and II are similar in that they recruited both patients and PCU operators. Paper III is a systematic review and the study presented in paper IV incorporates echocardiograms performed on patients included in paper II.

7.1.1 Paper I

In this prospective study at Oslo University Hospital, Rikshospitalet, patients already referred for elective echocardiography were asked to participate. Twenty-one medical students without previous echocardiographic experience, who were in their second half of medical school, were recruited at random from 104 applicants to perform PCU. All of them had completed a standardized 4-hour PCU training program prior to patient examination. The 72 patients asked to participate had been hospitalized for various cardiac disorders between February and March 2012. Written informed consent was obtained from all participants, both patients and students. Exclusion criteria included practical and medical considerations, such as lack of consent, short time span between scheduled procedures and post-procedural or hemodynamically unstable patients. Experienced echocardiographers working in the Department of Cardiology echocardiographic laboratory performed the subsequent SE blinded.

7.1.2 Paper II

All 26 internal medicine residents who were on call in our Medical Department at Vestfold Hospital Trust (during the study period from September 2011 to June 2012) received a standardized 2-hour PCU training and thereafter participated in the study. The only inclusion criterion for PCU patient screening was that the residents found a clinical indication to perform PCU, primarily upon patient admission, but also in hospitalized patients who

presented acute scenarios. The residents were to report results for up to 15 predefined cardiac landmarks. These were arbitrarily subdivided into 3 priority groups, such that left ventricle (LV) and pericardium were of first, valvular disease and aortic dilatation of second and right ventricle, both atria and vena cava inferior of third priority. A subsequent blinded SE was performed for reference by experienced echocardiographers. Exclusion from the reference SE mirrored those from paper I; poor PCU image quality (all four first priority landmarks not visualized), lack of informed consent, significant hemodynamic changes between PCU and SE (not predefined, but in each case decided by a consensus based on intravenous fluid administration, treatment with diuretics or other medications, or cessation or initiation of arrhythmias) or if the patient had been discharged before the SE could be performed.

7.1.3 Paper III

Paper III is a review article where we aimed to include studies with a direct comparison of contemporary echocardiographic systems. The studies referred to were to include patients being examined with both transthoracic 3DE and 2DE, and the results obtained with the two methods should have been validated against an acceptable reference standard.

Study participants should have been consecutively referred to echocardiography for assessment of either LV systolic function or valvular heart disease. We carefully scrutinized all selected papers for exclusion criteria applied for the 3DE study. It was anticipated that a selection bias in terms of patients was unavoidable given the known limitations of the 3DE method described above (i.e. patients with atrial fibrillation and conditions limiting the possibility of high quality imaging).

Since we aimed at evaluating real time 3DE, only original articles published between 2007 and 2012 were assessed for eligibility. Further details of this search are provided in the Additional file 1 of this paper.

7.1.4 Paper IV

In view of the anticipated results of the systematic search above, the study in paper IV was designed. Patients included in paper II who were eligible for the reference 2DE standard examination were examined with 3DE to evaluate LV volumes and EF. Although the purpose of this thesis was to reflect everyday clinical practice in a general hospital and patients were consecutively screened, a selection bias was unavoidable and feasibility of 3DE thus may be overestimated, since those subjected to a 3DE had been through both a PCU and a successful 2DE. Still, we chose the design presented since we also aimed at detecting possible differences in LV volume measurements obtained with the two methods. The study accordingly allowed a description of patient characteristics of those included versus those excluded from the LV measurements with 3DE.

7.2 Training for PCU

The 2002 ASE guidelines on echocardiographic training for non-cardiologists were too comprehensive for our training capacity, and more recent guidelines on this topic were not available when we designed the present studies. The training levels applied in the PCU studies available at that time [30, 31] were unrealistic for our purposes, and it was apparent that acceptable HCU performance had been reported by examiners with very limited training [13, 15]. Moreover, our aim was to present training course which all residents (and eventually for future residents) could attend; anticipating that a course requiring too many resources would be deemed unacceptable for hospital administrations, we chose the amount of training based upon the range of the latter two studies.

7.2.1 Medical students

Before entering the training course the medical students were encouraged to study a selection of video-loops provided for them, demonstrating normal cardiac anatomy and common pathology. The pre-course manual also featured a compendium describing the cardiac views

in ultrasound and how to position the transducer to obtain the different views. The course for six trainees at a time consisted of a 45 minute introduction to cardiac ultrasound, followed by 60 minutes to practice on one another (group of three with one scanner and a mentor). Furthermore, they had 75 minutes practice on patients in the cardiology ward (by themselves in groups of two with one scanner). This was followed by 60 minutes of case reviews, where recorded images were reviewed and discussed.

7.2.2 Residents

The training of residents was within the lowest range of the previous reports of HCU training. This was due to the anticipation that residents had a better basic knowledge of cardiac anatomy and disorders than medical students. In addition, due to limited resources we were unable to undertake a more comprehensive training program. The residents underwent a 2-hour training program. First, a bedside group session (5-6 residents per group), which included practical demonstrations of the PCU scanner and image acquisition from the apical (4-chamber, 2-chamber and long axis), parasternal (long axis) and subcostal views. This was followed by a 1-hour individual hands-on training session which also included the demonstration of a complete SE. During both sessions, image interpretation was explained according to the required evaluation protocol as described in table 1 of paper II.

7.3 Echocardiographic devices used in the thesis

7.3.1 Pocket-size ultrasound

The echocardiographic devices available during the course of this thesis, on which PCU operation is possible, were the Acuson P10 (Siemens Medical Solutions, PA, USA) and the Vscan (GE Vingmed Ultrasound, Horten, Norway). The former (weight 725 g) allows only 2D grey-scale imaging, whereas the latter (weight 390 g) also allows color-coded blood flow images. Neither of these systems have quantitative measurement facilities other than linear

distances. However, according to EAE recommendations the Acuson P10 is not strictly a pocket size imaging device given that it lacks a color Doppler function [19].

The Vscan is the basis of all PCU examinations performed in studies I and II, and the details pertaining to this apparatus are described in paper I. Further details of the PCU method are presented in detail in papers I and II, in particular table 1 of the latter.

7.3.2 Two dimensional echocardiography

2DE is used as the reference method for diagnostic accuracy in papers I and II. At Oslo University Hospital, Rikshospitalet it was performed with either a Vivid 7 or Vivid 9 scanner (GE Vingmed Ultrasound, Horten, Norway) and at Vestfold Hospital Trust exclusively with a Vivid 9 scanner. In both studies the echocardiographers performing these examinations were blinded to the result of the corresponding PCU examination.

7.3.3 Three dimensional echocardiography

All 3DE examinations in paper IV were undertaken with a Vivid 9 scanner by two echocardiographers with experience of using it. They were blinded to previous PCU and 2DE findings. The 3DE recordings were obtained within a maximum of 2 hours after the 2DE examinations. Volume calculations and EF were made with the on-board software (4D AutoLVQ) directly after image acquisition to reflect the use in a busy outpatient clinic. Although intrinsic automated border detection of the endocardium in end-diastole and end-systole was utilized, manual corrections were performed whenever found necessary by the echocardiographer, as applied in a previous study or reference values for 3DE derived LV volumes and EF [6].

7.4 The systematic review

As described, paper III explores current literature as to whether 3DE systems perform better than 2DE in assessment of LV volumes and valvular disease. Although not explicitly stated in

the publication, this review was conducted in accordance with the PRISMA statement [40] which is among the most widely recognised set of guidelines available to prepare and report review articles.

The systematic search is one of the key factors that distinguish systematic review articles from traditional review articles. The objective of a systematic search is to identify all the relevant literature about a topic and the quality of such a search is a critical point. It is not believed that a review article, systematic or not, is able to produce any medical truth. Yet, it provides a status for a medical problem at a given time on the basis of available evidence [41]. Most important, this method enables others to reproduce the search in detail.

7.5 Statistics

Papers I and II incorporate the PCU of a patient as the index test measured against a reference standard examination on the same patient. We chose 2DE as the reference standard, as it traditionally was used in patient management and recommended for the study of cardiac anatomy and function [39, 42-44]. To evaluate the performance of PCU we measured its diagnostic accuracy. The *STARD Statement for Reporting Studies of Diagnostic Accuracy* [45] states that diagnostic accuracy can be expressed in a number of ways. The term accuracy refers to the amount of agreement between the results from the index test and those from the reference standard, where the latter is to reflect the true disease status of each patient [46]. To this end we chose to express PCU diagnostic accuracy as the sensitivity and specificity with the corresponding positive and negative predictive values when prevalence is taken into account. These concepts are elaborated upon elsewhere [47].

In papers I and IV we studied the feasibility of PCU and 3DE respectively:

In paper I, feasibility was evaluated by a retrospective quality assessment performed by two experienced echocardiographers who reviewed all recorded PCU and SEs in a blinded

fashion. These recordings were then classified as good, fair or poor, seeking to determine the proportion of images adequate for interpretation. Examinations graded as good or fair were sufficient to this end. It is important to note that feasibility, in this context, does not reflect the opinion of the students' as to what extent they were able to perform PCU either partially or at all. Nor is it a measure of the proportion of patients for whom it is possible to obtain PCU images from. Feasibility should rather be seen as the proportion of apparently successful examinations verified to be of diagnostic quality. This quality assessment is explained in detail in the paper.

In paper IV, feasibility is defined as the proportion of patients referred for echocardiography successfully examined with 2DE for whom it was possible to obtain 3DE images of sufficient quality. Reasons for exclusion from the 3DE studies are described in detail in paper IV.

Furthermore, paper IV sought to evaluate the agreement between 3DE (which prospectively was defined as reference due to its status in contemporary recommendations [48]) and 2DE. This was done as first described by Bland and Altman: *Statistical methods for assessing agreement between two methods of clinical measurement* published in this form in the Lancet in 1986 [49], by the increasingly accepted Bland-Altman analysis and plot.

7.6 Ethics

All three clinical studies were approved by Regional Committees for Medical and Health Research Ethics in Norway (reference no. 2011-1403 for paper I and 2010/3234 for paper II and IV).

8 Summary of results

8.1 Paper I

In this paper we investigated whether a brief, group-based PCU training course would allow medical students to improve their ability to detect clinically relevant cardiac lesions at the bedside. In total, 72 patients were included and 110 examinations were performed. The mean time for physical examination (PE) was 7 ± 2 minutes and 17 ± 6 minutes for PCU.

With a stethoscope, sensitivity to detect clinically relevant (moderate or greater) valvular disease was 29% for mitral regurgitation, 33% for aortic regurgitation, and 67% for aortic stenosis. PCU improved sensitivity to detect mitral regurgitation (69% $p < 0.001$). However, sensitivity to detect aortic regurgitation (43%) and aortic stenosis (70%) did not improve significantly. Specificity was $\geq 89\%$ for all valvular diagnoses by both methods. For non-valvular diagnoses, PCU sensitivity to detect moderate or greater left ventricular dysfunction (90%) was excellent, detection of right ventricular dysfunction (79%) was good, while detection of dilated left atrium (53%), dilated right atrium (49%), pericardial effusion (40%), and dilated aortic root (25%) was less accurate. Specificity varied from 57% to 94%.

In the retrospective quality assessment for feasibility a total of 22% of all PCU examinations were of poor image quality, 41% were characterized as fair and the remaining 38% as good. In contrast, 92% of the reference echocardiograms were of good quality, while 8% were fair.

8.2 Paper II

In this study we wanted to assess the diagnostic accuracy of the pocket-size ultrasound device when used by unselected residents with minimal training working on call in a medical department to detect relevant cardiac pathology at acute admissions.

During a 9.2 months period a total of 435 patients were screened, and a flow chart showing those patients screened with PCU subsequently found to be eligible for reference standard examination (n = 303) is presented as fig. 1 in this paper. The majority of patients were included on the basis of presenting with chest pain or suspected heart failure.

The number of performed examinations by resident varied from 1 to 57. One resident did not perform any examinations. By priority landmarks, the fraction of total patients examined for first priority was 92% and for second and third priority 63% and 59% respectively.

In the pooled LV and pericardial (1st priority) data, sensitivity/specificity/positive predictive value (PPV)/negative predictive value (NPV) were 61/92/70/89 % respectively. Similar specificities and NPVs were observed for the 11 remaining indices, as were lower sensitivities and PPVs. The best PCU sensitivity (76%) was attained for the assessment of LV wall motion abnormalities. Overall agreement was $k = 0.50$.

8.3 Paper III

In this systematic review of studies published between 2007 and 2012, we investigated whether 3DE systems would perform better than 2DE in the transthoracic echocardiographic assessment of LV volumes and valvular disease in general cardiology care.

The review was presented with full electronic search strategy and a total of 836 original articles were identified, of which 35 were screened for eligibility. The predefined process for selecting studies was described and hence 20 studies from 18 publications were included for analysis.

The results for LV assessment and reproducibility were clearly in favour of 3DE. In valvular heart disease the advantage of 3DE was also apparent, but far less convincing due to patient selection, methodological problems and the application of questionable *gold standards*.

The study did identify common reasons for excluding patients from comparison between 2DE and 3DE. However, these were infrequently reported and thus no feasibility data could be presented.

8.4 Paper IV

This study investigated the feasibility of 3DE in patients at a general hospital for LV studies already completed by 2DE and explored the agreement between the two methods.

Of 273 consecutive patients examined with 2DE, 202 (74%) had satisfactory 3DE images for LV volume and EF measurements. Reasons for exclusion of 71 patients from the 3DE study included irregular heart rhythm in 58 patients and poor quality images in 13 patients.

Median LV end-diastolic volume was 146 mL with 3DE and 161 mL with 2DE ($p < 0.001$). The respective values for LV end-systolic volume were 76 mL and 83 mL ($p < 0.001$), and for LVEF 48% and 49% ($p = 0.061$). Pearson correlation coefficient for LV end diastolic volume (EDV), LV end systolic volume (ESV) and LVEF was 0.775, 0.877 and 0.820 respectively.

Bland–Altman plots including regression lines for all LV parameters showed the bias and limits of agreement for LVEDV, LVESV and LVEF to be 15.9 mL (-63.1 to 94.9), 6.0 mL (-41.0 to 53.0) and 1.16 % points (-12.8 to 15.1) respectively. The model indicated that in patients with LVEF < 36 % measured with 3DE, 2DE had a tendency to underestimate LVEF. Conversely, LVEF was overestimated in patients with LVEF ≥ 36 %.

9 Discussion

9.1 Pocket-size cardiac ultrasound

The main findings in paper I were that PCU improves medical students' ability to detect mitral regurgitation over and above physical examination, and that the PCU method helped students detect moderate or severe LV dysfunction visualized by a high sensitivity.

Statements in paper II were of a fair diagnostic accuracy in terms of studies of systolic LV function and a strong negative predictive value for nearly all studied indices.

These two studies are similar in design but not directly comparable in terms of operator selection, training protocols and patient selection and characteristics. They both study minimally trained non-cardiologists in their acquisition and interpretation of cardiac ultrasound with a pocket-size device. As is the norm in older HCU studies [30, 31] and more recent PCU studies [50-52] a safe cut off for training and education is difficult to ascertain, even though Prinz and coworkers argue that such a level exists [53].

The question of training has been debated for several years. In 2010, Feldman et al. stated the following: *"The evidence does not support the use of hand-carried ultrasound by hospitalists"* [54]. This was based upon the use of laptop sized HCU devices and notably before the era of pocket-size imaging devices, but still, the main concerns behind this statement are relevant and are listed as follows:

- The lack of large multicenter studies of HCU use by hospitalists leaves many questions unanswered, including cost-effectiveness and patient-centered benefit
- Standard echocardiography cannot be circumvented by a hospitalist-operated HCU
- A major problem with the HCU literature is its lack of standardization between – and within – studies leaving comparison generalization of results impossible

- It has not been determined how much training would be optimal in order to achieve levels of accuracy that are acceptable

After the Vscan device was presented in 2009, these discussions were revitalized and shortly afterwards, the EAE (now EACVI) presented their position statement [19] which lists a classification of current available echo machines, along with the already mentioned key points for the use of the pocket-size devices.

In 2013, the ASE published an expert consensus statement on FCU [55]. The applicability of this statement, in itself, is not defined by which type of imaging device one uses. FCU is presented more as a term for the type of examination and the factors required, among these the specific training. To elaborate: FCU can be performed on full size equipment, with an altogether different threshold for operation than what has given grounds for our introduction of PCU. Although the components of a training program are presented (i.e. training environment, didactic education, hands-on training and image interpretation) the ASE refrains from making specific recommendations for the documentation of competency (i.e. hours and amount of training).

Relevant to Norwegian hospitals and the Norwegian Society of Cardiology is the 2014 EACVI position paper on *Focus cardiac ultrasound*, abbreviated FoCUS [56]. This paper summarizes targets, scenarios and conditions where PCU has been shown to perform relatively safe. Furthermore, a reference to the EACVI recommendations for emergency echocardiography [57] is made as to highlight the presented list of emergency cardiovascular diseases/conditions to be included in additional learning programmes for non-cardiologists, when training for emergency echocardiography. As for specific training requirements, the EACVI states that:

Knowing the complexity of the topic and diversity of medical professionals who undergo training in FoCUS, it seems unlikely that strictly predefined minimal number of hours of hands-on image acquisition training or the number of personally performed and/or interpreted cases would ever fit for all.

Also, it is mentioned that the number of required hours/studies should be evaluated according to standardized accreditation. Thus, the key responsibility for FoCUS training and accreditation lies in the hands of the operators' speciality organization or scientific body.

Before even attempting to define an adequate level of training for a group, the purpose of PCU has to be clear; do we aim to examine for the presence or absence of disease, or is the primary goal to be able to determine the severity of disease.

In both PCU studies we investigated if the operators were able to detect *echocardiographic* disease. This, in turn, gives rise to two pressing questions; what if the PCU detects disease and what if it does not. The studies did not attempt to answer these questions to the full. It is, however, apparent that, given the high negative predictive values obtained in paper II, a negative (i.e. normal) PCU examination excludes echocardiographic disease with a high degree of certainty. This is not the same as to say that disease is excluded. Neither paper I nor paper II have assessed any possible presence or absence of disease where *all* clinical and para-clinical test results have been taken into account. In brief, the findings in the two PCU studies indicate that when PCU is used by minimally trained non-echocardiographers, a positive PCU examination as well as all cases of negative examinations but where clinical or para-clinical tests give suspicion of disease, the patient should be referred to a standard echocardiogram. This is a view shared by the 2013 ASE recommendations for FCU [55].

In the ASE guidelines on FCU [55] it is not excluded that training can begin at medical school, albeit it's clinical use should be limited to licensed physicians. Moreover, the FoCUS-

statement [56] does not include any specific comments on the use of PCU by medical students. Such a use is, however, supported by the 2011 EAE position paper [19].

Wittich et al. (2002) [32] used HCU as a supplement to traditional methods of teaching and instruction in medical school with the hypothesis that the devices could also be used to develop clinical reasoning skills. This view is supported by others [33, 58, 59].

In 2014, Andersen and coworkers trained a total of 30 medical students to use PCU as a supplement to their physical examination during their allocated hospital terms. The students were in their fifth year of medical school and received three evenings of hands-on training including three short lectures (<20 min) and were encouraged to perform at least 75 examinations prior to placement. The results were in fact superior to those we present in paper I and quite similar to those in paper II, with a strong negative predictive value although a much lower positive predictive value for cardiac diagnoses [60]. The results are not directly comparable given the different conditions in the three studies, but with the uniform finding of high negative predictive values it still seems plausible that the PCU method could be used to rule out certain conditions, given that the physical examination and other examination modalities point in the same direction.

In a study of PCU as an adjunct to clinical examination, Panoulas et al. [61] go further than our results indicate. They introduced five final-year medical students and three junior doctors without prior echocardiographic experience to PCU with a standardized 2-hour bedside tutorial. Subsequently they assessed 122 cardiology patients using history, physical examination, ECG and PCU. Their final clinical diagnosis was compared with that of a consultant clinician's and also an expert in echocardiography. A limitation of that study, however, was the lack of a proper reference method for PCU. Nonetheless, they found that even with a small amount of training, and to a certain degree a lack of clinical skill, PCU

improved the clinical diagnosis over and above history, physical examination and ECG findings.

In order to improve the design of that study, an ideal approach would be to assess PCU + physical examination versus physical examination alone in terms of clinical outcome. In this context, Lucas et al. [62] reported a comprehensive study of patients randomized to care guided by a laptop-size HCU (n = 226) versus usual care (n = 227). The primary outcome, the difference in length of stay, was not statistically significant. Whether or not the use of HCU or PCU affects care quality or has any long-term effect on either morbidity or mortality remains unknown.

9.2 Three dimensional echocardiography

In the systematic literature search presented in paper III, a prominent and interesting finding was that the feasibility of 3DE was largely unknown, even if the limitations of 3DE are clearly outlined. Real time 3DE has been available the past decade, but it was not until 2012 that it was recommended as routine for the evaluation of the left ventricle by the EAE/ASE [48]. These recommendations briefly mention the challenge of feasibility and accentuate the advantage related to the lack of geometric assumptions which is considered the drawback of the 2DE method.

In paper III, we also found that 3DE was preferable to 2DE when assessing LV volumes and EF given its superior reproducibility and better agreement with CMR. It is well accepted that both echocardiographic methods underestimate volumes in comparison with CMR [48, 63], but on the other hand there were divergent reports as to which of the two methods has the most pronounced underestimation.

In paper IV, the main findings were a feasibility of three quarters to perform 3DE successfully in patients who had undergone a diagnostic 2DE and that there was an overestimation of LV

volumes with 2DE when compared 3DE in the same patients. LV EF was similar with both methods.

The 3DE method for LV studies (4D AutoLVQ) utilized in the GE Vivid E9 system was validated using CMR as reference in a study by Muraru and coworkers [63]. Patients (n=103) referred for echo were selected on basis of acceptable image quality and stable sinus rhythm. Patients in unstable clinical conditions or with severely dilated ventricles were excluded. Regretfully, the study does not mention the number of patients excluded nor the volumes used as cut-off for exclusion. Given that patients with severely dilated ventricles are recommended regular echocardiographic follow up due to worse prognosis, this group is important and an evaluation of and validation for such patients should preferably have been included.

The validity of the 4D AutoLVQ method was also studied by Hansegård et al. [64]. Thirty-five patients with dilated LVs up to an end-diastolic volume of 243 mL (by 3DE) were included. Patients with atrial fibrillation, however, had been excluded. They did not use CMR for reference but instead TomTec 4D LV-Analysis (plug-in v.2.2), concluding that the method in question gave rapid and reproducible measurements of LV volumes and EF with good agreement.

Shibayama et al. studied 44 consecutive patients to determine the accuracy of 3DE to LV volume measurement as compared to 2DE and CMR (reference method) [65]. This study validated the 3DE method for Acuson SC2000 volume imaging ultrasound system (Siemens medical solutions USA Inc, Mountain View, CA, USA). Again an unknown number of patients were excluded due to irregular heart rhythm, in addition to metallic implants and claustrophobia. The feasibility of 3DE analyses in the selected study group were 93%.

This study included both fully- and semi-automated border detection to delineate the endocardial border. Bland-Altman analysis showed that both 2DE and 3DE underestimated

volumes when compared to CMR. The 3D semi-automated technique underestimated the least, whereas the fully automated volume determination underestimated the most, also compared to 2DE measurements. The latter trend is in keeping with the findings of paper IV. Such a trend was also reported in the aforementioned study by Muraru et al [63].

Highly relevant to the question of feasibility is an article published in 2012 by Thavendiranathan et al. [66]. By including 91 patients, 67 in sinus rhythm and 24 with atrial fibrillation, they compared a fully automated offline 3DE workflow to 2DE and CMR to evaluate LV volumes and EF. A total of 145 consecutive patients referred for echocardiography were screened: Ten refused to participate, 37 excluded on grounds of poor image quality (3 of these because of AF stitch artifacts) and 7 due to technical errors, leaving 67% feasibility, nearly identical to our finding reported in paper IV.

Interestingly, they observed the same pivotal tendency in EF measurements as we did in that study, although with the difference that 3DE was measured against CMR and their cut-off was arbitrarily set at 50%. 3DE underestimated more in the lower ranges of EF than in the higher. Compared to CMR, 3DE exhibited an underestimation of volumes (bias \pm limits of agreement) for EDV by -17.6 ± 52 mL, ESV -9.8 ± 35 mL and EF 0.3 ± 4.9 percentage points.

With the high number of patients not eligible for 3DE in mind, it would be of interest to know whether it is favorable to reduce the number of heart cycles needed for 3D imaging in order to increase feasibility. Marcon et al. [67] demonstrated in 2010 that the feasibility of 3DE was improved when using a 2-beat modality instead of multibeam, but the temporal resolution remained insufficient to provide an accurate estimation of LVEF.

Irregular heart rhythm is an independent exclusion factor not only from CMR, but, as presented in this thesis, it marginalizes the wide-spread applicability of 3DE. To our

knowledge, there are no studies presenting a comparison between 2DE and 3DE to determine the accuracy of LV measurements in patients with atrial fibrillation. When examining patients in this condition, 2DE does have its limitations as is reflected from the recommendation to use multiple beats contrary to single beat in patients with sinus rhythm [39]. Regarding the large number of patients with atrial fibrillation, such comparative studies are clearly of interest.

Contrary to our findings and the findings reported in the aforementioned studies, Hare et al [35] found no significant differences in LV volume estimations (nor in EF calculations) when comparing 2DE and 3DE. Like in our study (paper IV), a reference method (i.e. CMR) was not included, and the question of standardized endocardial tracing principles with the 2DE method was further actualized. The authors refer to previous work [68] which compared 3DE and CMR after myocardial infarction on 30 patients by correlation and Bland-Altman analyses, finding 3DE comparable to CMR, and thus supporting the validity of their conclusions.

Most contemporary studies report that 3DE underestimates volumes compared to CMR. Miller et al. argue that the degree of underestimation might have to do with suboptimal image quality [69]. Whether the same argument applies for 2DE versus 3DE is unknown.

In both 3DE papers (III and IV), we did make a point of possible vendor specific differences for 3DE volume calculations as a source of inter-study bias. This has been shown to be the case with myocardial 3DE LV deformation imaging [70], but it seems not to be the case for 3DE LV volume calculation [71]. The most probable explanation for different volumes measured between 2DE, 3DE and CMR still seem to be a diverging identification and tracing of the endocardium, as discussed in paper IV.

At present the 2DE technique is routinely used in transthoracic echocardiography, reference values have been available for many years and prognostic information guiding decision-

making processes are based on 2DE derived measurements. We have pointed out the lower feasibility of 3DE indicating that in one in four unselected patients adequate LV studies can only be performed with 2DE. Additionally, there are controversies in LV volume agreement between the two methods. These are issues which it is very important to have in mind when deciding management algorithms based upon 2DE and 3DE respectively. Cut-off values for management cannot simply and without debate be transferred from the 2DE world to 3DE, as most outcome studies are based on 2DE measurements. Although Caselli et al. [72] followed 178 patients for a median of 45 months and found that 3DE assessment of LV EF and volumes has the potential to predict major cardiovascular events when added to standard 2DE, it would be uncertain at best to extrapolate established 2DE treatment thresholds for 3DE measurements to this end.

10 Strengths and limitations

10.1 Strengths

10.1.1 PCU

The patient population in paper I could be criticized as it was chosen for cardiac pathology in a highly specialized department. This limits generalizability of the findings, but it is not really a limitation. The point of the study was to determine the accuracy and value of the training program in detecting disease, not demonstrating effectiveness in the real world of general clinical practice. The detection of disease requires disease to be present and thus the selected patient group suited the purpose of our study. No other inclusion or exclusion criteria were applied. In our opinion, the quality assessment performed gave a realistic impression of the actual quality differences between PCU and SE recordings in the study.

In paper II, patients admitted when residents were on call would normally have no other means of being examined with PCU (nor SE). By refraining from applying any inclusion or exclusion criteria for PCU, other than the resident on call finding grounds to perform one, a study of a near real life practice was enabled. All examinations included had been compared with a SE performed as soon as practically feasible, and the study is further strengthened by the strict exclusion criteria from a reference examination as reflected by the large number of excluded cases.

For both paper I and II, PCU operators (students/residents) in each study display a considerable heterogeneity in both knowledge of anatomy and physiology and in skill. This might be considered a limitation as it is the group that is studied (not really the patients or the device), and as certain aspects, between them the amount of self-study, remain undescribed. However, all operators had gone through the same standardized training program in each

study, and the fact still remains that this heterogeneity will most certainly be present regardless of a scientific study or not, reflecting the real world scenario.

To further reflect common practice, we chose to study the entire group of residents in our department without exception. The results presented are therefore not based on selected individuals, but are applicable to a realistic situation where the aim is to offer PCU by a heterogeneous group of residents in acute scenarios.

10.1.2 3DE

The review in paper III was carefully conducted according to the PRISMA recommendations, and with clear study inclusion criteria. Those assessed but excluded are described in detail in an additional file. All patients in the studies selected had been through both 2DE and 3DE evaluated against a *gold standard*.

In the prospective clinical study of patients who had undergone 2DE measurements the subsequent 3DE (paper IV), the reference 3DE was conducted after the shortest possible time span in order to avoid bias related to significant hemodynamic changes, patient discharge or transfer to another hospital for invasive management. All echocardiographic studies had been undertaken by experienced operators. Both methods had been through a careful evaluation in our department, including studies of accuracy and reproducibility [3] and reference values [4-6]. For 2DE we have also conducted an outcome study supporting the validity of our tracings for obtaining LV volumes with the biplane Simpson's method [73].

10.2 Limitations

10.2.1 PCU

Although the student selection criteria in paper I aimed to be at random, it is a fact that the applicants actually had shown an interest. This somewhat limits the generalizability of the results obtained by this otherwise randomly selected group.

The training in both PCU studies was intentionally minimal. As discussed, surprisingly good results had been reported prior to designing the studies, supporting the use of ultrasound by minimally trained students, residents and fellows in cardiology [13, 15, 21, 22, 30-34].

Nonetheless, these studies did not describe examinations of patients in acute stage settings, which leaves our choice of training protocol largely unfounded and to a certain degree inadequate. Although this was in our opinion comprehensive and demanding, this inadequacy is reflected in the quality control assessment performed, and a low sensitivity for diagnosing most cardiac disorders studied.

It is a fact that the study sample in paper II could have benefitted from inclusion of the many excluded patients: Those acutely transferred for treatment (i.e. invasive coronary angiography) or treated to a hemodynamic altered state from the time of PCU. Thus, the exclusion criteria in study II were both a strength to ensure accuracy to be measured as best possible, but also a limitation, as these patients were in the greatest need of prompt investigation and management, and to this end the PCU could have been pivotal. Also, there might have been examinations performed but not reported, with the ability to change the results. Furthermore, the study in paper II did not contain similar quality assessment as in paper I, and therefore a difference in the quality of recordings between PCU and 2DE was not studied. Finally, no attempts had been made to explore the additional clinical benefit of PCU upon PE alone.

10.2.2 3DE

Like in all reviews we cannot exclude the possibility of having overlooked some studies in paper III, and our quite strict criteria for inclusion might have rejected relevant studies. Since we did the search in 2012 a number of studies evaluating 3DE versus 2DE have been published, such that the review does not reflect the academic reality as of the beginning of 2015 at the completion of this thesis.

The study design described in paper IV aimed to reflect a real world scenario, but is hampered by the selection bias of patients undergoing 3DE. Patients included were probably first subjected to a selection for better acquisition-possibilities (i.e. easier to examine) through the PCU and thereafter a selection by exclusion from the 2DE. Therefore, our feasibility for 3DE may not reflect that of a truly unselected group. Problems connected to variable LV endocardial tracings with 2DE and manual editing of the 3DE derived automatic tracings are obvious and may explain the deviation of our results from those reported in other studies.

11 Perspectives

The high negative predictive ability yielded by PCU, even in the hands of fairly untrained operators, could be of value in patient management in terms of ruling out those with significant disease. But, in our experience, executing the training protocol and follow up of a large group of residents is rather time consuming and requires a great deal of staying power. Add to this the fact that there are no representative randomized trials and outcome studies neither supporting nor dissuading against the broad scale implementation of PCU in common hospital practice.

Such an implementation is not unrealistic although the constant work involved has to be taken into account. Conversely, the task of training might feasibly be given to universities educating medicine students, as even a short course has the potential to add information to the physical examination. The challenge will be to maintain the students' ability to continue with PCU as physicians practicing in the real world.

The 3DE method has to be improved to increase feasibility. To this end, an introduction of probes with smaller *footprint* and better temporal and spatial resolution allowing less demand for *echogenic* patients and patients with regular heart rhythm are tasks to overcome. 2DE is still a solid diagnostic tool which should be available when 3DE fails. This implies that both methods should be retained. The old saying is still applicable: It is futile to put all your eggs into one basket.

Finally, the introduction of 3DE does require a fair amount of training for its implementation as it, in our opinion, demands additional skills to those required to perform 2DE. In addition, old concepts of normal values and cut-off for management reserved for 2DE have to be redefined or at the very least re-evaluated, as they are not immediately interchangeable with 3DE measurements.

12 Conclusions

1. PCU with a pocket-sized scanner allowed a selection of medical students to detect clinically relevant mitral regurgitation significantly better compared with physical examination. However, the detection of aortic regurgitation and aortic stenosis suffered from considerable underestimation of severity and accordingly did not improve significantly. LV dysfunction was also detected with high sensitivity. Although the group model educated a large number of students in an effective manner, the small number of training scans per student limited performance and prolonged acquisition times.
2. We found PCU to be infrequently used by residents, and with an overall low sensitivity. A fair diagnostic accuracy was observed for LV systolic function and LV wall motion abnormalities, which were arbitrarily chosen as first priority evaluation landmarks. The PCU method provides a suitable means of ruling out significant disease, as was reflected in its high specificity and NPV.
3. LV systolic function should ideally be assessed with 3DE in patients with good quality images and a regular heart rhythm. A substantial number of patients, however, will still have to be examined with 2DE for this indication. Due to patient selection, methodological problems and lack of acceptable *gold standards*, the evidence supporting the notion that 3DE is superior to 2DE in terms of the evaluation of valvular heart disease in general practice is still somewhat limited.
4. One fourth of patients who had undergone 2DE for assessment of the LV could not undergo 3DE assessment, mostly due to atrial fibrillation. A significant overestimation of LV volumes was observed in 2DE compared to 3DE, whereas no such difference was found for LVEF.

13 Reference list

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